Synthesis and Antimicrobial Activity of Some 1,3-Disubstituted Indeno[1,2-*c*]pyrazoles

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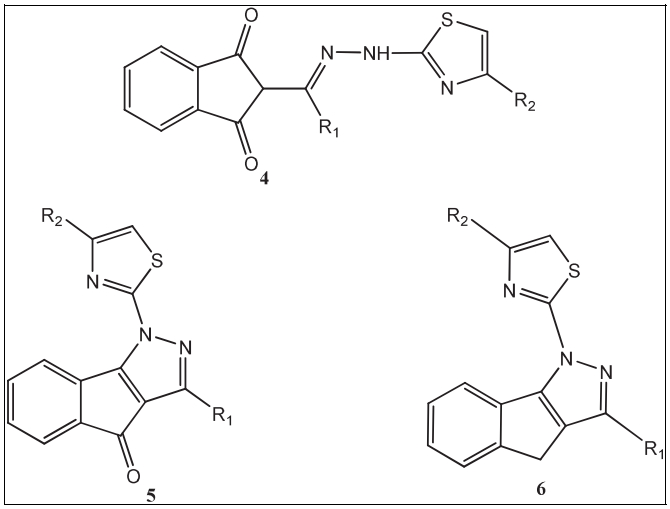

Synthesis of new 3-alkyl indeno[1,2-*c*]pyrazoles, possessing 4-substituted thiazole moiety at position-1 derived from 2-acyl indane-1,3-diones, has been described. These compounds and their precursor were screened for their antibacterial (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*) and antifungal (*Aspergillus niger*, *Candida albicans*) activities.

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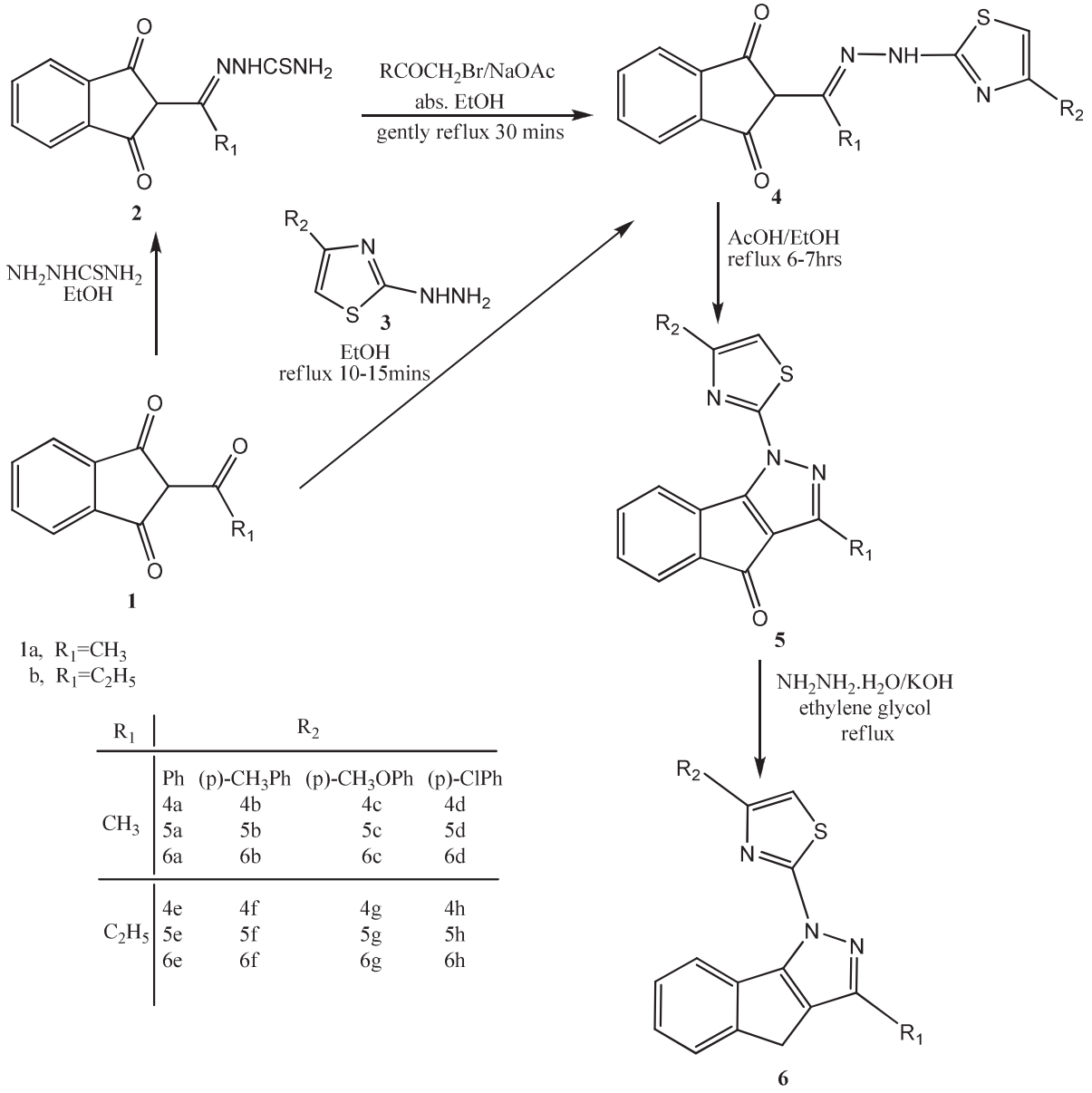
INTRODUCTION

Pyrazole derivatives have played a crucial role in the history of heterocyclic chemistry and have been used extensively as important pharmacophores and synthons, because they are known to possess a broad spectrum of biological properties such as antimalarial [1], antidepressant [2], hypoglycemic [3], and so on. Introducing a pyrazolidinone ring [4] in place of the β-lactam ring (in penicillins and cephalosporins) [5] results in enhanced activity. Owing to their versatile chemotherapeutic importance, a significant amount of research effort has been focused on pyrazole nucleus. Among the pyrazoles fused to carbocyclic and heterocyclic ring systems, indenopyrazoles occupy a unique position because of wide ranging biological activities such as antihypertensive [6], anticancer [7], herbicidal [8], antibacterial [9], antiviral [10], and so on associated with them. On the other hand, sulfur and/or nitrogen heterocycles that possess pharmaceutical activities widely occur in nature in the form of alkaloids, vitamins, pigments, as constituents of plant and animal cells and other bioactive natural products [11]. Thiazoles and their derivatives were especially reported to possess analgesic [12], antitumor [13], antimicrobial [14], anti-inflammatory [15], antipyretic [16], antitubercular [17], antiHIV [18], diuretic [19], anticonvulsant [20] activities, and so on. Antimicrobial activities of some substituted thiazoles are well established, because they possess (S C N) toxophoric unit. The designing of new types of polyheterocyclic compounds along with the refining of procedures for synthesis of these known substances is an urgent target of the modern heterocyclic chemistry. The need of making a large number of variously substituted indenopyrazoles for biological screening led the chemist to develop numerous methods of synthesis [21, 22] in the past. Realizing the importance of the above biodynamic heteryl nuclei, and in continuation of our interest in designing the synthesis of biologically active nitrogen and sulfur heterocycles, it was planned to synthesize a system thiazolyl indenopyrazole that combines together two biolabile components, which are indenopyrazole and 4-substituted thiazole, therefore, report herein, the synthesis and antimicrobial (antibacterial and antifungal) activity of 16

Scheme 1



R_1	R_2			
	Ph	(p)-CH_3Ph	(p)-CH_3OPh	(p)-ClPh
CH_3	4a	4b	4c	4d
	5a	5b	5c	5d
	6a	6b	6c	6d
C_2H_5	4e	4f	4g	4h
	5e	5f	5g	5h
	6e	6f	6g	6h

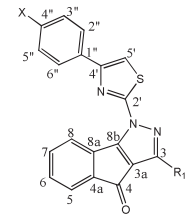
new 3-alkyl indeno[1,2-*c*]pyrazoles, possessing 4-substituted thiazole moiety at position-1 (**5** and **6**) and eight key hydrazones (**4**) derived from 2-acyl indane-1,3-diones (**1**).

RESULTS AND DISCUSSION

2-Acyl indane-1,3-diones (**1**) needed for the purpose were prepared by the Claisen condensation of $RCOCH_3$ and diethylphthlate under the influence of sodium methoxide according to the literature procedure [23]. Condensation of equimolar quantities of 2-acylindane-1,3-dione (**1**) with thiosemicarbazide in boiling absolute ethanol yielded the corresponding thiosemicarbazones [24] in excellent yields, which on treatment with different 4-substituted phenacyl bromides afforded the corresponding key hydrazones (**4**) [25] in high yields. The hydrazones on cyclization in boiling absolute alcohol in presence of glacial acetic acid furnished pyrazoles (**5**) in good yields. The indenopyrazoles (**5**) have also been obtained by the condensation of the 2-acylindane-1,3-dione (1) with 2-hydrazino-4-substituted thiazoles, which first afforded hydrazones (**4**) and then underwent cyclization in presence of glacial acetic acid to afford pyrazoles (**5**). The assumption that the condensation of the thiosemicarbazide/hydrazine has occurred on the side chain carbonyl and not on 1- or 3-position of indan-1,3-dione moiety finds support from the results reported the literature [21b–d,26]. The indenopyrazoles (**5**) on Wolf–Kishner reduction [27]

Table 1

^{13}C-NMR chemical shifts of indenopyrazoles (**5**).



Compd. (Indenopyrazoles)	C_3	C_{3a}	C_4	C_{4a}	C_5	C_6	C_7	C_8	C_{8a}	C_{8b}	$C_{2'}$	$C_{4'}$	$C_{5'}$	$C_{1''}$	$C_{2'',6''}$	$C_{3'',5''}$	$C_{4''}$	R_1 (CH_3/C_2H_5) CH_3	R_1 (CH_3/C_2H_5) CH_2	X(CH_3/OCH_3)
5a	149.07	122.96	184.22	133.89	123.64	128.72	133.71	123.91	140.27	157.37	159.71	154.29	109.88	132.25	128.93	126.01	130.23	12.61	–	–
5b	148.17	123.41	184.14	133.30	123.93	130.40	132.52	124.14	140.13	157.41	159.61	153.26	109.78	131.25	125.97	129.61	138.49	12.66	–	21.34
5c	148.13	123.43	184.20	133.34	123.90	130.44	132.65	124.21	140.20	157.45	159.70	153.04	108.81	126.89	127.38	114.29	159.89	12.68	–	55.40
5d	148.91	123.09	184.91	134.10	123.68	127.61	132.93	124.42	140.12	157.37	159.89	153.65	109.50	131.79	128.40	129.12	133.78	12.70	–	–
5e	153.02	122.91	183.67	133.87	123.79	128.45	133.14	124.02	140.02	157.55	159.78	154.09	110.49	132.59	128.86	125.97	130.28	12.40	21.05	-
5f	153.29	122.96	183.90	133.31	123.91	130.42	132.81	124.17	140.23	157.80	159.82	154.32	109.82	131.33	126.00	129.63	138.50	12.50	21.10	21.35
5g	152.99	122.77	183.69	133.42	123.83	130.50	132.72	124.07	140.11	157.66	159.84	154.08	109.13	123.81	127.35	114.3	159.95	12.44	21.01	55.37
5h	153.12	121.70	183.99	134.50	124.12	127.70	133.21	124.87	140.02	157.43	160.10	154.13	109.70	131.44	128.86	129.84	133.92	12.51	21.20	–

Table 2

In vitro antimicrobial activity (*pMIC) of compounds **4a–h**, **5a–h**, and **6a–h**.

	Antibacterial activity			Antifungal activity	
Compounds	*B. subtilis*	*S. aureus*	*E. coli*	*C. albicans*	*A. niger*
4a	1.159	1.460	1.460	1.460	1.460
4b	1.477	1.778	1.477	1.176	1.477
4c	0.893	1.495	1.495	1.194	1.495
4d	1.184	1.786	1.786	1.485	1.485
4e	1.176	1.176	1.176	1.477	1.477
4f	1.493	1.493	1.493	1.493	1.493
4g	0.908	1.510	1.510	1.510	1.510
4h	1.213	1.815	1.514	1.514	1.514
5a	1.137	1.438	1.438	1.137	1.438
5b	1.15	1.150	1.455	1.455	1.455
5c	1.173	1.474	1.474	1.474	1.474
5d	1.479	1.479	1.479	1.479	1.479
5e	1.455	1.455	1.455	1.455	1.455
5f	1.171	1.472	1.171	1.472	1.472
5g	1.189	1.490	1.490	1.490	1.496
5h	1.194	2.098	1.796	1.796	1.495
6a	1.420	1.119	1.420	1.420	1.420
6b	1.438	1.438	1.438	1.438	1.739
6c	1.458	1.458	1.458	1.458	1.759
6d	1.764	1.462	1.462	1.462	1.462
6e	1.739	1.739	1.438	1.438	1.438
6f	1.455	1.756	1.756	1.455	1.455
6g	1.474	1.775	1.474	1.474	1.775
6h	1.479	1.780	1.780	1.780	1.479
Norfloxacin	2.698	2.698	2.698	–	–
Fluconazole	–	–	–	3.000	3.000

*pMIC = –log MIC.

yielded the corresponding indenopyrazoles (**6**) in moderate yields (Scheme 1).

All the newly synthesized compounds, hydrazones (**4**) and indenopyrazoles (**5** and **6**), were well characterized by satisfactory spectroscopic (IR, ^{1}H-NMR, ^{13}C-NMR, and mass) and analytical data (vide experimental). The most characteristic feature of the IR spectra of hydrazones (**4**) was that they displayed absorption bands of medium intensity in the region at 3365–3271 cm^{-1} (N H and O H stretch) and >C O and >C N sharp absorptions in region 1689–1682 cm^{-1} and 1641–1629 cm^{-1}, respectively. The ^{1}H-NMR spectra of hydrazones (**4**) displayed ^{1}H signal due to NH (exchangeable with deuterium oxide) in the region δ 12.33–13.03; however, the signal due to C_2 H could not be located. The aromatic protons were observed in the region δ 6.91–8.10 and aliphatic CH_3 protons of ethyl group and CH_2 protons of propyl group present on C_2-1*H*-indene-1,3(2*H*)-diones appeared in the regions at δ 2.81–2.91 and 3.19–3.23, respectively. Further, the ratio of aromatic to aliphatic protons was found satisfactory (vide experimental). The IR spectra of indenopyrazoles (**5**) exhibited strong >C O stretching in the region 1708–1702 cm^{-1} due to conjugated five-membered cyclic ketone [27a,28a]. The main characteristic feature of ^{1}H-NMR spectra of these indenopyrazoles (**5**) is the downfield shifting of C_8 H (δ 8.38–8.46) when compared with other aromatic protons due to anisotropic-diamagnetic effect of lone pair of electrons present on nitrogen and sulfur of N_1-thiazole moiety [28]. The C_3 CH_3 and C_3 CH_2 protons of ethyl group were observed in the region at δ 2.38–2.41 and 2.67–2.79, respectively. The other aromatic and aliphatic protons were observed in the expected regions. The C_3 *CH_3* and C_3 *CH_2*CH_3 protons showed upfield shift [29] relative to the corresponding protons in the hydrazones (**4**) coupled with the observation that the IR spectra displayed strong absorption bands in the region 1708 1702 cm^{-1} unequivocally proves that cyclization of the hydrazones (**4**) has led to the formation of indenopyrazoles (**5**). An examination of ^{13}C-NMR spectra of indenopyrazoles (**5**) displayed signals in most downfield region at δ 183.66–184.12 corresponding to the C_4 carbons [30] and the signals in the regions at δ 148.17–153.29, δ 121.70–123.43, and δ 157.37–157.80 are in agreement with the value recorded for the carbon atoms C_3, C_{3a}, and C_{8b} of pyrazole ring [31], respectively. The chemical shifts in regions at δ 159.61–160.10($C_{2'}$), δ 153.26–154.32($C_{4'}$), and δ 109.13–110.49($C_{5'}$) corroborate the thiazole character of N_1-thiazole moiety [32]. The chemical shift signals in aromatic regions at δ 123.64–124.12, δ 127.61–130.50, δ 132.59–133.71, and δ 123.91–124.87 corresponds to C_5, C_6, C_7, and C_8, respectively, which are

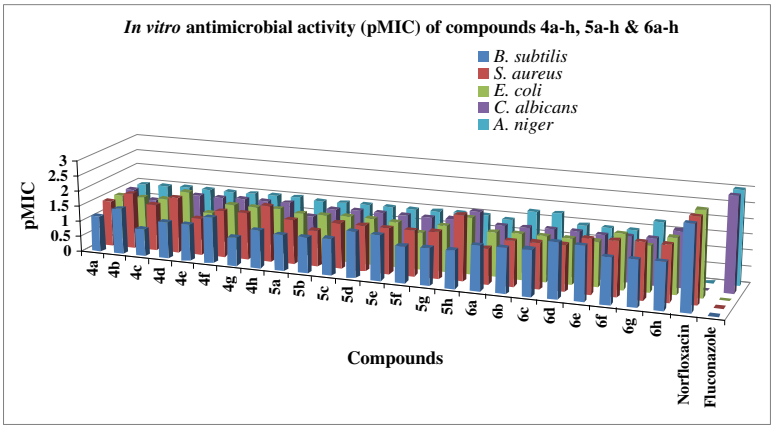


Figure 1. *In vitro* antimicrobial activity (pMIC) of compounds **4a–h**, **5a–h**, and **6a–h**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

in agreement with the results reported in literature [30]. The signals of other aliphatic and aromatic carbons were observed in the expected region (Table 1).

The IR spectra of indenopyrazoles (**6**) displayed strong absorptions in the region at 1544–1534 cm^{-1} presumably due to endo CN, which is supported by the values assigned in literature [33]. The disappearance of >C O stretch due to conjugated five-membered cyclic ketone in IR spectra of indenopyrazoles (**6**) as exhibited by indenopyrazoles (**5**) and appearance of singlets in ^{1}H-NMR spectra in the region δ 3.63–3.67 (2H) assignable to C_4 protons along with downfield shifting of C_8 H (δ 8.64–8.84) presumably due to increased anisotropic-diamagnetic effect of N_1-thiazole moiety as the hybridization state of C_4 changes from sp^2 to sp^3 confirms Wolf–Kishner reduction of **5→ 6** (>C O → $>CH_2$). The other aromatic protons, however, appeared in the expected regions (vide experimental). Further, the mass spectral data and analytical data of **4**, **5**, and **6** are in agreement with their molecular formula.

All the 24 newly synthesized compounds **4a–h**, **5a–h**, and **6a–h** were tested *in vitro* for their antimicrobial activity against two Gram-positive bacteria, that is, *Bacillus subtilis* (MTCC 441) and *Staphylococcus aureus* (MTCC 7443), one Gram-negative bacteria, that is, *Escherichia coli* (MTCC 42), and two fungi, that is, *Candida albicans* (MTCC 183) and *Aspergillus niger* (MTCC 282). Serial tube dilution technique [34] was used to determine minimum inhibitory concentration (MIC). pMIC equals to negative logarithm of MIC was calculated (Table 2).

Most of the compounds exhibited moderate to good antimicrobial activity against the tested microorganisms. In comparing their pMIC values with Norfloxacin, all the compounds were effective against *E. coli*, and compounds **4d**, **5h**, and **6f** especially showed very high activity. All the compounds were effective against *S. aureus* but compounds **4b**, **4d**, **4h**, **5h**, **6e**, **6f**, **6g**, and **6h** exhibited very high activity. Compound **5h** displayed inhibitory activity almost similar to Norfloxacin against *S. aureus*, whereas compounds **4e**, **5b**, and **6a** exhibited moderate level of activity. Compounds **4c** and **4g** were less effective against *B. subtilis*, whereas compounds **4a**, **4d**, **4e**, **4h**, **5f**, **5g**, and **5h** were found moderatively active in comparison with Norfloxacin. All the newly synthesized compounds (**4a–h**, **5a–h**, and **6a–h**) were assayed for antifungal activity. Compounds **5h** and **6h** exhibited strong antifungal activity against *C. albicans* and compounds **4b**, **4c**, and **5a** showed moderate activity in comparing their pMIC with Fluconazole, whereas compounds **6b**, **6c**, and **6g** displayed very strong activity against *A. niger*. A careful analysis of pMIC data shows some interesting trends. Comparison of pMIC data of N_1-thiazolyl hydrazones (**4a–h**) and N_1-thiazolylindenopyrazoles (**5a–h** and **6a–h**) revealed that the cyclization of hydrazones (**4**) to pyrazoles (**5**,**6**) leads to significant increase in their antimicrobial activity (Fig. 1). The potent antimicrobial activity exhibited by **4d**, **4h**, **5d**, **5h**, **6d**, and **6h** may be due to the presence of 4-chlorophenyl pharmacophore at C_4 of the thiazole moiety. The present study highlights the importance of indenopyrazole and 4-substituted thiazole ring features responsible for the inhibitory action against the microorganisms and, therefore, may serve as a lead molecule for further modifications to obtain clinically useful novel entities.

CONCLUSION

In conclusion, we have prepared successfully eight new N_1-thiazolyl hydrazones (**4a–h**) and 16 indenopyrazoles (**5a–h** and **6a–h**) using easily obtainable compounds 1-, 2-, 3-, and 4-substituted phenacyl bromides under environmentally benign conditions and their *in vitro* antimicrobial activities were evaluated. The compounds containing 4-chlorophenyl pharmacophore at C_4 of the thiazole moiety (**4d**, **4h**, **5d**, **5h**, **6d**, and **6h**) exhibited significant antimicrobial activities.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The IR absorption spectra were scanned on Perkin Elmer Spectrum, BX II FTIR spectrometer using potassium bromide (KBr) pellets, and the wave numbers were given in cm^{-1}. The ^{1}H-NMR spectra and ^{13}C-NMR were recorded on Bruker Avance II 400 spectrometer at 400 and 100 MHz, respectively, in $CDCl_3$ or $CDCl_3$ + DMSO-d_6 or DMSO-d_6. The chemical shifts are reported in parts per million (δ, ppm) using tetramethylsilane (TMS) as an internal standard. Coupling constants *J* are valued in Hertz (Hz). Mass spectra were recorded on Waters Micromass Q-Tof Micro (ESI) spectrometer. Elemental analysis was carried out using Vario Micro Cube Elementar CHNS analyser. Analytical results for C, H, N, and S were within ±0.4% of the theoretical values. The purities of the compounds were checked by thin layer chromatography (TLC) using readymade silica gel (SIL G/UV_{254}, ALUGRAM) plates. The spots were visualized under ultraviolet (UV) lamp. Solvents were dried using standard literature procedures. 2-Acyl indane-1,3-diones (**1**) [23] and 2-hydrazino-4-substituted thiazoles (**3**) [35] were prepared according to literature procedures. Norfloxacin (GMH Laboratories, Baddi, H. P., India) and fluconazole (Aurobindo Pharmaceuticals, Mandal, A. P., India) were used as reference antimicrobial agents against the tested microorganisms.

Synthesis of thiosemicarbazone of 2-acyl indane-1,3-diones (2a and 2b). The thiosemicarbazones **2** were prepared by condensation of equimolar quantities of 2-acyl indane-1,3-dione (**1**) and thiosemicabazide in absolute alcohol as per literature procedure [24].

Synthesis of 2-(1-(2-(4-phenylthiazol-2-yl)hydrazono) ethyl)-1*H*-indene-1,3(2*H*)-dione (4a). To a suspension of **2a** (1.30 g, 5 mmol) and sodium acetate (0.41 g, 5 mmol) in absolute ethanol (25 mL), phencyl bromide (0.99 g, 5 mmol) was added slowly with stirring, and the reaction mixture was gently refluxed for 30 min and then allowed to stand at room temperature. The yellowish solid thus obtained was filtered and washed with ethanol to give **4a** in excellent yield 1.49 g (83%), mp 202–204°C; IR (KBr): NH 3357, CO 1687, CN 1643 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.81 (s, 3H, CH_3), 7.22–7.69 (m, 8H, ArH and 5′-thiazole H), 7.73–7.76 (m, 2H, 4-, and 7-H), 12.33 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 360.09 $(M)^+$. *Anal*. Calcd. for $C_{20}H_{15}N_3O_2S$: C, 66.46; H, 4.18; N, 11.63; S, 8.87. Found: C, 66.74; H, 3.83; N, 11.70; S, 9.26.

Following exactly the same procedure as detailed in **4a,** the other hydrazones **4b**–**h** were prepared from the corresponding *p*-substituted phenacyl bromides and thiosemicarbazones of 2-acyl indane-1,3-dione (**2**). The physical, spectral, and analytical data for these compounds are given as follows.

2-(1-(2-(4-*p*-Tolylthiazol-2-yl)hydrazono)ethyl)-1*H*-indene-1,3(2*H*)-dione (4b). The compound **4b** was obtained as orange yellow solid, 79% yield, mp 214–216°C; IR (KBr): NH 3354, CO 1682, CN 1641 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 2.91 (s, 3H, CH_3), 7.23–7.74 (m, 7H, ArH, and 5′-thiazole H), 7.99–8.02 (m, 2H, 4- and 7-H), 13.03 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 398.21 $(M+Na)^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19; S, 8.54. Found: C, 66.84; H, 4.33; N, 10.85; S, 8.93.

2-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)ethyl)-1*H*-indene-1,3(2*H*)-dione (4c). The compound **4c** was obtained as orange yellow solid, 84% yield, mp 230–232°C; IR (KBr): NH 3271, CO 1684, CN 1637 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.85 (s, 3H, CH_3), 3.83 (s, 3H, OCH_3), 6.92–7.74 (m, 7H, ArH, and 5′-thiazole H), 8.03-8.06 (m, 2H, 4- and 7-H), 13.03 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 392.12 $(M+H)^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3O_3S$: C, 64.43; H, 4.38; N, 10.73; S, 8.19. Found: C, 64.29; H, 4.27; N, 11.03; S, 8.57.

2-(1-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)ethyl)-1*H*-indene-1,3(2*H*)-dione (4d). The compound **4d** was obtained as yellow solid, 80% yield, mp 250–252°C; IR (KBr): NH 3290 CO 1687, CN 1633 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.91 (s, 3H, CH_3), 7.33–7.74 (m, 7H, ArH and 5′-thiazole H), 8.08–8.10 (m, 2H, 4-, and 7-H), 13.01 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 395.05 $(M)^+$, 396.11 $(M+1)^+$, 397.21 $(M+2)^+$. *Anal*. Calcd. for $C_{20}H_{14}ClN_3O_2S$: C, 60.68; H, 3.56; N, 10.61; S, 8.10. Found: C,60.35; H, 3.86; N,10.95; S, 8.32.

2-(1-(2-(4-Phenylthiazol-2-yl)hydrazono)propyl)-1*H*-indene-1,3(2*H*)-dione (4e). The compound **4e** was obtained as orange yellow solid, 84% yield, mp 184–186°C; IR (KBr): NH 3353, CO 1686, CN 1629 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.29 (t, 3H, ethyl-CH_3), 3.23 (q, 2H, ethyl-CH_2), 7.60 (m, 8H, ArH, and 5′-thiazole H), 8.07–8.09 (m, 2H, 4- and 7-H), 12.98 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 375.1 $(M)^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3O_2S$: C, 67.18; H, 4.56; N, 11.19; S, 8.54. Found: C, 66.79; H, 4.17; N, 11.05; S, 8.73.

2-(1-(2-(4-*p*-Tolylthiazol-2-yl)hydrazono)propyl)-1*H*-indene-1,3(2*H*)-dione (4f). The compound **4f** was obtained as orange yellow solid, 81% yield, mp 206–208°C; IR (KBr): NH 3365, CO 1683, CN 1638 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, 3H, ethyl-CH_3), 2.35 (s, 3H, CH_3), 3.20 (q, 2H, ethyl-CH_2), 7.18–7.62 (m, 7H, ArH, and 5′-thiazole H), 7.64–7.66 (m, 2H, 4- and 7-H), 12.34 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 390.1 $(M+H)^+$. *Anal*. Calcd. for $C_{22}H_{19}N_3O_2S$: C, 67.84; H, 4.92; N, 10.79; S, 8.23. Found: C, 68.07; H, 4.72; N, 10.43; S, 7.87.

2-(1-(2-(4-(4-Methoxyphenyl)thiazol-2-yl)hydrazono)propyl)-1*H*-indene-1,3(2*H*)-dione (4g). The compound **4g** was obtained as orange yellow solid, 81% yield, mp 200–202°C; IR (KBr): NH 3267, CO 1683, CN 1633 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, 3H, ethyl-CH_3), 3.23 (q, 2H, ethyl-CH_2), 3.82 (s, 3H, OCH_3), 6.91–7.78 (m, 9H, ArH, and 5′-thiazole H), 12.39 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 406.11 $(M+H)^+$. *Anal*. Calcd. for $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.07; H, 4.39; N, 10.21; S, 7.82.

2-(1-(2-(4-(4-Chlorophenyl)thiazol-2-yl)hydrazono)propyl)-1*H*-indene-1,3(2*H*)-dione (4h). The compound **4h** was obtained as orange yellow solid, 83% yield, mp 216–218° C; IR (KBr): NH 3346, CO 1689, CN 1637 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.28 (t, 3H, ethyl-CH_3), 3.19 (q, 2H, ethyl-CH_2), 7.36–7.65 (m, 7H, ArH, and 5′-thiazole H), 7.78–7.80 (m, 2H, 4- and 7-H), 12.98 (br s, 1H, NH, deuterium oxide exchangeable); ms: (TOF MS ES$^+$) *m/z* 409.07 $(M)^+$, 410.07 $(M+1)^+$, 411.07 $(M+2)^+$. *Anal*. Calcd. for $C_{21}H_{16}ClN_3O_2S$: C, 61.53; H, 3.93; N, 10.25; S, 7.82. Found: C, 61.47; H, 4.21; N, 9.98; S, 8.01.

The thiazolyl hydrazones **4a**–**h** were also prepared by refluxing the equimolar mixture of 2-acyl indane-1,3-dione (**1**; 5 mmol) and 2-hydrazino-4-substituted thiazoles (**3**; 5 mmol) in dry ethanol for 15–20 min. The mixture was cooled, filtered, washed with cold

ethanol, and air-dried to give yellow solid, yield 1.66 g (92%) of **4a**, 1.67 g (89%) of **4b**, 1.77 g (91%) of **4c**, 1.71 g (91%) of **4d**, 1.70 g (91%) of **5e**, 1.75 g (90%) of **5f**, 1.80 g (89%) of **5g**, and 1.91 g (93%) of **5h**. The physical, spectral, and analytical data for these compounds correspond to thiazolyl hydrazones **4a**–**h** synthesized by earlier method.

Synthesis of 3-methyl-1-(4-phenylthiazol-2-yl)indeno [1,2-*c*]pyrazol-4(1*H*)-one (5a). The hydrazone **4a** (1.80 g, 5 mmol) was refluxed in a solution of 75 mL ethanol-acetic acid (2:1) for 5 h. The reaction mixture was concentrated, and the precipitates thus obtained were separated by filtration, which on recrystallization from chloroform afforded yellow needles of **5a**, yield 1.25 g (73%); mp 210–212°C; IR (KBr): CO 1702, CN 1607 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.39 (s, 3H, CH_3), 7.39–7.59 (m, 6H, ArH), 7.76 (s, 1H, 5′-Thiazole H), 7.97 (d, 2H, 2″-, 6″-H, *J* = 7.76 Hz), 8.46 (dd, 1H, 8-H, *J* = 7.16, 2.41 Hz); ^{13}C-NMR (DMSO-d_6): δ 12.61, 109.88, 122.96, 123.64, 123.91, 126.01, 128.72, 128.93 130.23, 132.25, 133.71, 133.89, 140.27, 149.07, 154.29, 157.37, 159.7, 184.22; ms: (TOF MS ES$^+$) *m/z* 344.09 $(M+H)^+$. *Anal*. Calcd. for $C_{20}H_{13}N_3OS$: C, 69.95; H, 3.82; N, 12.24; S, 9.34. Found: C, 69.73; H, 3.46; N, 11.96; S, 9.22.

Following exactly the procedure as employed for **5a**, the indenopyrazoles **5b**–**h** were synthesized from the corresponding hydrazones **4b**–**h**. The physical, spectral, and analytical data for these compounds are given as follows.

3-Methyl-1-(4-*p*-tolylthiazol-2-yl)indeno[1,2-*c*]pyrazol-4 (1*H*)-one (5b). The compound **5b** was obtained as yellow needles (chloroform), 71% yield, mp 208–210°C; IR (KBr): CO 1707, CN 1621 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 2.41 (s, 3H, CH_3), 7.30 (d, 2H, 3″-, 5″-H, *J* = 7.95 Hz), 7.39–7.41 (m, 1H, 6-H), 7.51–7.55 (m, 2H, 5-, 7-H), 7.62 (s, 1H, 5′-H), 7.83 (d, 2H, 2″-, 6″-H, *J* = 7.96 Hz), 8.42 (dd, 1H, 8-H, *J* = 7.56, 2.40 Hz); ^{13}C-NMR ($CDCl_3$): δ 12.66, 21.34, 109.78, 123.41, 123.93, 124.14, 125.97, 129.61, 130.40, 131.25, 132.59, 133.30, 138.49, 140.13, 148.17, 153.26, 157.41, 159.61, 184.14; ms: (TOF MS ES$^+$) *m/z* 380.3 $(M+Na)^+$. *Anal*. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76; S, 8.97. Found: C, 70.31; H, 4.13; N,12.15; S, 9.29.

1-(4-(4-Methoxyphenyl)thiazol-2-yl)-3-methylindeno [1,2-*c*]pyrazol-4(1*H*)-one (5c). The compound **5c** was obtained as yellow needles (chloroform), 75% yield, mp 204–206°C; IR (KBr): CO 1708, CN 1606 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.38 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.03 (d, 2H, 3″-, 5″-H, *J* = 8.40 Hz), 7.39–7.42 (m, 1H, 6-H), 7.53–7.57 (m, 3H, 5-, 7-, and 5′-thiazole H), 7.88 (d, 2H, 2″-, 6″-H, *J* = 8.44 Hz), 8.42 (dd, 1H, 8-H, *J* = 7.4, 2.41 Hz); ^{13}C-NMR ($CDCl_3$): δ 12.68, 55.40, 108.81, 114.29, 123.43, 123.90, 124.21, 126.89, 127.38, 130.44, 132.65, 133.34, 140.20, 148.23, 153.04, 157.45, 159.70, 159.89, 184.20; ms: (TOF MS ES$^+$) *m/z* 396.3 $(M+Na)^+$. *Anal*. Calcd. for $C_{21}H_{15}N_3O_2S$: C, 67.54; H, 4.05; N, 11.25; S, 8.59. Found: C, 67.32; H, 4.11; N, 11.57; S, 8.78.

1-(4-(4-Chlorophenyl)thiazol-2-yl)-3-methylindeno[1,2-*c*] pyrazol-4(1*H*)-one (5d). The compound **5d** was obtained as yellow needles (chloroform), 69% yield, mp 240–242°C; IR (KBr): CO 1708, CN 1635 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.41 (s, 3H, CH_3), 7.37–7.40 (m, 1H, 6-H), 7.48 (d, 2H, 2″-, 6″-H, *J* = 8.24 Hz), 7.52–7.57 (m, 3H, 5-,7-, and, 5′-thiazole H), 7.89 (d, 2H, 3″-, 5″-H, *J* = 8.2 Hz), 8.38 (dd, 1H, 8-H, *J* = 7.20, 2.43 Hz); ^{13}C-NMR (DMSO-d_6): δ 12.7, 109.5, 123.09, 123.68, 124.42, 127.61, 128.40, 129.12, 131.79, 132.93, 133.78, 134.10, 140.12, 148.91, 153.65, 157.37, 159.89, 184.91; ms: (TOF MS ES$^+$) *m/z* 377.01 $(M)^+$, 378.3 $(M+1)^+$, 379.04 $(M+2)^+$; *Anal*. Calcd. for $C_{20}H_{12}ClN_3OS$: C, 63.57; H, 3.20; N, 11.12; S, 8.49. Found: C, 63.21; H, 3.57; N, 10.92; S, 8.59.

3-Ethyl-1-(4-phenylthiazol-2-yl)indeno[1,2-*c*]pyrazol-4 (1*H*)-one (5e). The compound **5e** was obtained as yellow needles (chloroform), 74% yield, mp 148–150°C; IR (KBr): CO 1703 cm^{-1}, CN 1610 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.35 (t, 3H, ethyl-CH_3), 2.67 (q, 2H, ethyl-CH_2), 7.14–7.41 (m, 7H, 5′-thiazole H and ArH), 7.74 (d, 2H, 2″-, 6″-H, *J* = 7.12 Hz), 8.41 (dd, 1H, 8-H, *J* = 7.32, 2.27 Hz); ^{13}C-NMR ($CDCl_3$): δ 12.40, 21.05, 110.49, 122.91, 123.79, 124.02, 125.97, 128.45, 128.86, 130.28, 132.59, 133.14, 133.87, 140.02, 153.0, 154.09, 157.55, 159.78, 183.67; ms: (TOF MS ES$^+$) *m/z* 358.6 $(M+H)^+$; *Anal*. Calcd. for $C_{21}H_{15}N_3OS$: C, 70.57; H, 4.23; N, 11.76; S, 8.97. Found: C, 70.69; H, 4.07; N, 11.60; S, 8.69.

3-Ethyl-1-(4-*p*-tolylthiazol-2-yl)indeno[1,2-*c*]pyrazol-4 (1*H*)-one (5f). The compound **5f** was obtained as yellow needles (chloroform), 65% yield, mp 160–162°C; IR (KBr): CO 1702, CN 1609 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H, ethyl-CH_3), 2.41 (s, 3H, CH_3), 2.75 (q, 2H, ethyl-CH_2), 7.21–7.31 (m, 4H, 5′-thiazole H and ArH), 7.40 (m, 1H, 7-H), 7.53 (d, 1H, 5-H, *J* = 7.24 Hz), 7.75 (d, 2H, 2″-, 6″-H, *J* = 8.16 Hz), 8.39 (dd, 1H, 8-H, *J* = 7.40, 2.32 Hz); ^{13}C-NMR ($CDCl_3$): δ 12.50, 21.10, 21.35, 109.82, 122.96, 123.91, 124.17, 126.0, 129.63, 130.42, 131.33, 132.81, 133.31, 138.50, 140.23, 153.29, 154.32, 157.80, 159.82, 183.90; ms: (TOF MS ES$^+$) *m/z* 394.3 $(M+Na)^+$. *Anal*. Calcd. for $C_{22}H_{17}N_3OS$: C, 71.14; H, 4.61; N, 11.31; S, 8.63. Found: C, 69.99; H, 4.47; N, 10.98; S, 8.33.

3-Ethyl-1-(4-(4-methoxyphenyl)thiazol-2-yl)indeno[1,2-*c*] pyrazol-4(1*H*)-one (5g).. The compound **5g** was obtained as yellow needles (chloroform), 73% yield, mp 154–156°C; IR (KBr): CO 1702, CN 1610 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.32 (t, 3H, ethyl-CH_3), 2.76 (q, 2H, ethyl-CH_2), 3.88 (s, 3H, OCH_3), 7.00 (d, 2H, 3″-, 5″-H, *J* = 8.22 Hz), 7.25–7.52 (m, 4H, 5′-thiazole H and ArH), 7.82 (d, 2H, 2″-, 6″-H, *J* = 8.24 Hz), 8.40 (dd, 1H, 8-H, *J* = 7.12, 2.29 Hz); ^{13}C-NMR (DMSO-d_6): δ 12.44, 21.01, 55.37, 109.13, 114.30, 122.77, 123.30, 123.81, 124.07, 127.35, 130.50, 132.72, 133.42, 140.11, 152.99, 154.08, 157.66, 159.84, 159.95, 183.69; ms: (TOF MS ES$^+$) *m/z* 388.4 $(M+H)^+$. *Anal*. Calcd. for $C_{22}H_{17}N_3O_2S$: C, 68.20; H, 4.42; N, 10.85; S, 8.28.Found: C, 68.57; H, 4.21; N, 10.73; S, 8.39.

1-(4-(4-Chlorophenyl)thiazol-2-yl)-3-ethylindeno[1,2-*c*] pyrazol-4(1*H*)-one (5h). The compound **5h** was obtained as yellow needles (chloroform), 72% yield, mp 210–212°C; IR (KBr): CO 1702, CN 1629 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.34 (t, 3H, ethyl-CH_3), 2.79 (q, 2H, ethyl-CH_2), 7.39–7.57 (m, 6H, 5′-thiazole H, and ArH), 7.88 (d, 2H, 3″-, 5″-H, *J* = 8.12Hz), 8.39 (d, 1H, 8-H, *J* = 7.54, 2.32 Hz); ^{13}C-NMR (DMSO-d_6): δ 12.51, 21.2, 109.7, 121.7, 124.12, 124.87, 127.70, 128.86, 129.84, 131.44, 133.21, 133.92, 135.50, 140.02, 153.12, 154.13, 157.43, 160.10, 183.99; ms: (TOF MS ES$^+$) *m/z* 392.3 $(M+1)^+$, 393.04 $(M+2)^+$, 394.3$(M+3)^+$. *Anal*. Calcd. for $C_{21}H_{14}ClN_3OS$: C, 64.36; H, 3.60; N, 10.72; S, 8.18. Found: C, 64.26; H, 3.87; N, 11.17; S, 8.53.

Synthesis of 2-(3-methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-phenylthiazole (6a). The solution of indenopyrazole **5a** (0.34 g, 1 mmol), ethylene glycol (5 mL), hydrazine hydrate (1 mL), and KOH (0.5 mL) was heated to 120°C for 1 h and at 180°C for 4 h. Thereafter, the reaction mixture was poured in cold water, the solid thus obtained was filtered, washed with water,

dried and recrystallized from benzene to give colorless needles of **6a** in moderate yield 174 mg (53%); mp 160–162°C; IR (KBr): CN 1535 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3), 3.63 (s, 2H, 4-H), 7.18–7.60 (m, 7H, 5′-thiazole H and ArH), 7.93 (d, 2H, 2″-, 6″-H, *J* = 7.8 Hz), 8.79 (dd, 1H, 8-H, *J* = 7.5, 2.37 Hz); ms: (TOF MS ES$^+$) *m/z* 352.1 (M+Na)$^+$. *Anal*. Calcd. for $C_{20}H_{15}N_3S$: C, 72.92; H, 4.59; N, 12.76; S, 9.73. Found: 73.04; H, 4.28; N, 12.46; S, 9.76.

Following exactly the procedure as detailed for synthesis of **6a**, the indenopyrazoles **6b**–**h** were prepared from the corresponding indenopyrazoles **5b**–**h**. The physical, spectral, and analytical data of these compounds are given as follows.

2-(3-Methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-*p*-tolylthiazole (6b). The compound **6b** was obtained as colorless crystals (benzene), 57% yield, mp 196–198°C; IR (KBr): CN 1542 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 2.42 (s, 3H, CH_3), 2.56 (s, 3H, CH_3), 3.67 (s, 2H, 4-H), 7.13–7.53 (m, 6H, 5′-thiazole H and ArH), 7.88 (d, 2H, 2″-, 6″-H, *J* = 5.7 Hz), 8.82 (dd, IH, 8-H, *J* = 7.2, 2.50 Hz); ms: (TOF MS ES$^+$) *m/z* 366.2 (M+Na)$^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3S$: C, 73.44; H, 4.99; N, 12.23; S, 9.34. Found: C, 73.19; H, 4.98; N, 11.56; S, 9.58.

4-(4′-Methoxyphenyl)-2-(3-methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl) thiazole (6c). The compound **6c** was obtained as colorless crystals (benzene), 55% yield, mp 180–182°C; IR (KBr): CN 1537 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 3.65 (s, 2H, 4-H), 3.86 (s, 3H, OCH_3), 7.20–7.79 (m, 6H, 5′-thiazole H and ArH), 7.93 (d, 2H, 2″-, 6″-H, *J* = 8.4 Hz), 8.74 (dd, 1H, 8-H, *J* = 7.5, 2.41 Hz); ms: (TOF MS ES$^+$) *m/z* 360.1 (M+H)$^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3OS$: C, 70.17; H, 4.77; N, 11.69; S, 8.92. Found: C, 69.82; H, 4.81; N, 12.01; S, 8.63.

4-(4-Chlorophenyl)-2-(3-methylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)thiazole (6d). The compound **6d** was obtained as colorless crystals (benzene), 51% yield, mp 174–176°C; IR (KBr): CN 1534 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 2.33 (s, 3H, CH_3), 3.65 (s, 2H, 4-H), 7.34–7.59 (m, 5H, ArH), 7.94 (s, IH, 5′-thiazole H), 8.01 (d, 2H, 3″-,5″-H, *J* = 7.5 Hz), 8.64 (dd, 1H, 8-H, *J* = 7.8, 2.37 Hz); ms: (TOF MS ES$^+$) *m/z* 364.1 (M+H)$^+$, 365.03 (M+2)$^+$, 366.1 (M+3)$^+$, 386.1 (M+Na)$^+$. *Anal*. Calcd. for $C_{20}H_{14}ClN_3S$: C, 66.02; H, 3.88; N, 11.55; S, 8.81. Found: C, 65.73; H, 4.18; N, 11.21; S, 8.73.

2-(3-Ethylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-phenylthiazole (6e). The compound **6e** was obtained as colorless crystals (benzene), 51% yield, mp 174–176°C; IR (KBr): CN 1534 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.39 (t, 3H, ethyl-CH_3), 2.82 (q, 2H, ethyl-CH_2), 3.66 (s, 2H, 4-H), 7.29–7.56 (m, 7H, 5′-thiazole-H and ArH), 7.99 (d, 2H, 2″-, 6″-H, *J* = 7.8 Hz), 8.83 (dd, 1H, 8-H, *J* = 7.5, 2.51 Hz); ms: (TOF MS ES$^+$) *m/z* 344.2 (M+H)$^+$. *Anal*. Calcd. for $C_{21}H_{17}N_3S$: C, 73.44; H, 4.99; N, 12.23; S, 9.34. Found: C, 73.74; H, 4.73; N, 11.97; S, 9.19.

2-(3-Ethylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-*p*-tolylthiazole (6f). The compound **6f** was obtained as deep red needles (benzene), 53% yield, mp 158–160°C; IR (KBr): CN 1544 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, ethyl-CH_3), 2.43 (s, 3H, CH_3), 2.83 (q, 2H, ethyl-CH_2), 3.65 (s, 2H, 4-H), 7.30 (d, 2H, 3″-, 5″-H, *J* = 8.1 Hz), 7.47–7.82 (m, 4H, 5′-thiazole-H and ArH), 8.03–8.06 (d, 2H, 2″-, 6″-H, *J* = 8.1 Hz), 8.84 (dd, 1H, 8-H, *J* = 7.5, 2.50 Hz); ms: (TOF MS ES$^+$) *m/z* 358.1 (M+H)$^+$, 380.1 (M+Na)$^+$. *Anal*. Calcd. for $C_{22}H_{19}N_3S$: C, 73.92; H, 5.36; N, 11.75; S, 8.97. Found: C, 73.88; H, 5.23; N, 12.17; S, 9.12.

2-(3-Ethylindeno[1,2-*c*]pyrazol-1(4*H*)-yl)-4-(4-methoxyphenyl) thiazole (6g). The compound **6g** was obtained as colorless crystals (benzene), 57% yield, mp 196–198°C; IR (KBr): CN 1534 cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 1.39 (t, 3H, ethyl-CH_3), 2.83 (q, 2H, ethyl-CH_2), 3.66 (s, 2H, 4-H), 3.81 (s, 3H, OCH_3), 7.17–7.82 (m, 6H, 5′-thiazole H and ArH), 8.04 (d, 2H, 2″-, 6″-H, *J* = 8.4 Hz), 8.80 (dd, 1H, 8-H, *J* = 7.5, 2.57 Hz); ms: (TOF MS ES$^+$) *m/z* 374 (M+H)$^+$. *Anal*. Calcd. for $C_{22}H_{19}N_3OS$: C, 70.75; H, 5.13; N, 11.25; S, 8.59. Found: C, 70.46; H, 5.52; N, 10.91; S, 8.94.

4-(4-Chlorophenyl)-2-(3-ethylindeno[1,2-*c*]pyrazol-1(4*H*)-yl) thiazole (6h). The compound **6h** was obtained as green needle-like crystals (benzene), 49% yield, mp 120–122°C; IR (KBr): CN 1537 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.38 (t, 3H, ethyl-CH_3), 2.82 (q, 2H, ethyl-CH_2), 3.64 (s, 2H, 4-H), 7.22–7.54 (m, 6H, 5′-thiazole H and ArH), 7.90 (d, 2H, 3″-, 5″-H, *J* = 8.4 Hz) 8.76 (dd, 1H, 8-H, *J* = 7.5, 2.70 Hz); ms: (TOF MS ES$^+$) *m/z* 378.1 (M+H)$^+$, 379.2 (M+2)$^+$, 380.1 (M+3)$^+$, 400.1 (M+Na)$^+$. *Anal*. Calcd. for $C_{21}H_{16}ClN_3S$: C, 66.75; H, 4.27; N, 11.12; S, 8.49. Found: C, 67.07; H, 4.28; N, 10.80; S, 8.79.

ANTIMICROBIAL ACTIVITY

All the 24 newly synthesized compounds **4a**–**h**, **5a**–**h**, and **6a**–**h** were screened for their *in vitro* antimicrobial activity against five microorganisms, two Gram-positive bacteria *B. subtilis* (MTCC 441) and *S. aureus* (MTCC 7443) and one Gram-negative bacteria *E. coli* (MTCC 42) and two fungi *C. albicans* (MTCC 183) and *A. niger* (MTCC 282) by serial tube dilution technique [33] using two solid media double strength nutrient broth and Sabouraud dextrose broth for bacterial and fungal growth, respectively. The stock solutions (100 μg/mL) of all the test compounds were prepared by dissolving 1 mg of the test compound in 10 mL of dimethylsulfoxide. Norfloxacin and Fluconazole were used as reference against bacteria and fungi, respectively. The fresh cultures were obtained by inoculation of respective microorganisms in suitable medium (double strength nutrient broth in case of bacteria and Sabouraud dextrose broth in case of fungi) followed by incubation at 37 ± 1°C. The stock solutions of the test compounds were serially diluted in test tubes containing 1 mL of sterile medium to get the concentration of 50–3.12 μg/ml and then inoculated with 100 μL of suspension of respective microorganism in sterile saline. The inoculated test tubes were incubated at 37 ± 1°C for 24 h in case of *B. subtilis*, *S. aureus*, and *E. coli*, at 37 ± 1°C for 48 h in case of *C. albicans* and at 37 ± 1°C for 120 h in case of *A. niger*, and their pMICs (−log of MICs) were determined. MIC, in microbiology, is the lowest concentration of an antimicrobial agent that will inhibit the visible growth of a microorganism after incubation.

The reference compounds Norfloxacin and Fluconazole were also tested under similar conditions to compare the results of tested compounds. The data for the antibacterial and antifungal studies are listed in Table 2.

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REFERENCES AND NOTES

[1] Kumar, S.; Kumar, G.; Kapoor, M.; Surolia, A. Synth Commun 2006, 36, 215.

[2] Palaska, E.; Aytemir, M.; Uzbay, T.; Erol, D. Eur J Med Chem 2001, 36, 539.

[3] Smith, D.; Forest, A.; Dulin, W. E. J Med Pharm Chem 1965, 8, 350.

[4] (a)Boyd D. B. InTheoretical and Physicochemical Studies on β-Lactam Antibiotics in β-Lactam Antibiotics Chemistry and Biology; Morin, R. B.;Gorman, M., Eds.;Academic Press:New York, 1982; Vol. 1, pp 437–545; (b)Jungheim, L. N.; Sigmund, S. K.; Jones, N. D.; Swartzend, J. K. Tetrahedron Lett 1990, 28, 285.

[5] (a) Jungheim, L. N.; Sigmund, S. K.; Fisher, J. W. Tetrahedron Lett 1987, 28, 285; (b) Jungheim, L. N.; Sigmund, S. K.; Jones, N. D.; Swartzendruber, J. K. Tetrahedron Lett 1987, 28, 289.

[6] Coombs, R. V.; Houlihan, W. J. U.S. Pat. 3,843,665; Chem Abstr 1975, 82, 57687b.

[7] (a) Matsuo, Y; Takehara, H; Tanimura, K; Takagi, T.; Nishida, S. Jpn Kokai Tokkyo Koho JP 62,99,361 (1987); Chem Abstr 1987, 107, 198315a; (b) Faidallah, H. M.; Al-Saadi, M. S.; Rostom, S. A. F.; Fahmy, H. T. Y. Med Chem Res 2007, 16, 300; (c) Rostom, S. A. F. Bioorg Med Chem 2006, 14, 6475.

[8] Pasteris, R. J; Muthukrishnan, R. Eur. Pat. EP 203,679 (1986); Chem Abstr 1987, 106, 71132f.

[9] Abdel-Wahab, B. F.; Abdel-Aziz, H. A.; Ahmed, E. M. Eur J Med Chem 2009, 44, 2632.

[10] El-Sabbagh, O. I.; Baraka, M. M.; Ibrahim, S. M.; Pannecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Rashad, A. A. Eur J Med Chem 2009, 44, 3746.

[11] (a) Dondoni, A.; Marra, A. Chem Rev 2004, 104, 2557; (b) Jin, Z. Nat Prod Rep 2005, 22, 196.

[12] Kalkhambkar, R. G.; Kulkarni, G. M.; Shivkumar, H.; Rao, N. R. Eur J Med Chem 2007, 42, 1272.

[13] Ramla, M. M.; Omar, M. A.; El-Khamry, A. M. M.; El-Diwan, H. I. Bioorg Med Chem 2006, 14, 7324.

[14] (a) Ozdemir, A.; Zitouni, G. T.; Kaplancikh, Z. A.; Revial, G.; Guven, K. Eur J Med Chem 2007, 42, 403; (b) Xin, Z.; Yang-fang, Z.; Jia, W.; Wei, J.; Liang, H.;Ping G. Chem Res Chinese U 2006, 22, 459; (c) Vicini, P.; Geronikaki, A.; Anastasia, K.; Incerti, M.; Zani, F. Bioorg Med Chem 2006, 14, 3859; (d) Dundar, O. B.; Ozgen, O.; Mentese, A.; Altanlar, N.; Ath, O.; Kendj, E.; Ertan, R. Bioorg Med Chem 2007, 15, 6012; (e) Cukurovali, A.; Yilmaz, I.; Gur, S.; Kazaz, C. Eur J Med Chem 2006, 41, 201.

[15] (a) Kumar, A.; Rajput, C. S.; Bhati, S. K. Bioorg Med Chem 2007, 15, 3089; (b) Holla, B. S.; Malini, K. V.; Rao, B. S.; Sarojini, B. K.; Kumari, N. S. Eur J Med Chem 2003, 38, 313.

[16] Pignatello, R.; Mazzone, S.; Panico, A. M.; Mazzone, G.; Penissi, G.; Castano, R.; Matera, M.; Blandino, G. Eur J Med Chem 1991, 26, 929.

[17] Ashtekar, D. R.; Fernandes, F.; Khadse, B. G.; Shirodkar, M. V. A. Chemotherapy 1987, 33, 22.

[18] Maass, G.; Immendoerfer, U.; Koenig, B.; Leser, U.; Mueller, B.; Goody, R.; Pfatt, B. Antimicrob Agents Chemother 1993, 37, 2612; (b) Maass, G.; Immendoerfer, U.; Koenig, B.; Leser, U.; Mueller, B.; Goody, R.; Pfatt, B. Antimicrob Agents Chemother 1993, 37, 2612.

[19] Andreani, A.; Rambaldi, M.; Mascellani, G.; Rugarli, P. Eur J Med Chem 1987, 22, 19.

[20] Amin, K. H.; Rahman, A. D. E.; Al-Erayani, Y. A. Bioorg Med Chem 2006, 14, 6475.

[21] Mosher, W. A.; Soeder, R. W. J Heterocycl Chem 1971, 8, 855; (b) Mosher, W. A.; Bechara, I. S. J Heterocycl Chem 1970, 7, 843; (c) Mosher, W. A.; Bank, T. E. J Heterocycl Chem 1971, 9, 1005; (d) Mosher, W. A.; Meier, W. E. J Org Chem 1970, 35, 3685; (e) Lemke, T. L.; Sawhney, K.; Lemke, B. K. J Heterocycl Chem 1982, 19, 363; (e) Belevich, E. M.; Gudriniece, E.; Paulins, J. Latv PSR Zinat Akad Vestis Khim Ser 1974, 226; (f) Hamilton, R. W. J Heterocycl Chem 1976, 13, 545.

[22] (a) Priede, J.; Gudriniece, E. Latv PSR Zinat Akad Vestis Khim Ser 1978, 579; (b) Coombs, R. V.; Houlihan, W. J. U.S. Pat. 3,843,665; Chem Abstr 1975, 82, 57694y; (c) Habeck, D. A.; Houlihan, W. J. U.S. Pat. 3,932,420; Chem Abstr 1976, 84, 121821m.

[23] (a) Kilgore, L. B.; Ford, J. H.; Wolfe, C. W. Ind Eng Chem 1942, 34, 494; (b) Shapiro, L.; Geiger, K.; Freedman, L. J Org Chem 1960, 25, 1860; (c) Dhawan, S. N.; Dasgupta, S.; Mor, S.; Gupta, S. C. Indian J Heterocycl Chem 1993, 2, 155.

[24] Sawhney, K. N.; Lemke, T. L. J Org Chem 1983, 48, 4326.

[25] (a) Easmon, J.; Heinisch, G.; Hofman, J.; Langer, T.; Grunicke, H. H.; Fink, J.; Purstinger, G. Eur J Med Chem 1997, 32, 397; (b) Siddiqui, N.; Arshad, M. F.; Khan, S. A. Acta Pharmaceutica-Drug Res 2009, 66, 161.

[26] Braun, R. A.; Mosher, W. A. J Am Chem Soc 1958, 80, 2749.

[27] (a) Gupta, S. C.; Quarishi, M. A.; Dhawan, S. N. Indian J Chem B 1979, 18, 547; (b) Quarishi, M. A.; Thakur, V. K.; Dhawan, S. N. Indian J Chem B 1989, 28, 891.

[28] (a) Dhawan, S. N.; Mor, S.; Sharma, K.; Chawla, A. D.; Saini, A.; Gupta, S. C. Indian J Chem B 1994, 33, 38; (b) Quarishi, M. A.; Thakur, V. K.; Dhawan, S. N. Indian J Chem B 1989, 28, 891; (c) Quarishi, M. A.; Dhawan, S. N. J Chem Eng Data 1989, 134; (d) Hamilton, R. W. J Heterocycl Chem 1976, 13, 545; (e) Mandel, A. N.; Bhattacharya, S. Indian J Chem B 1984, 23, 736.

[29] Lemke, T. L.; Cramer, M. B.; Shanmugam, P. J Pharm Sci 1978, 67, 1377.

[30] (a) Patra, A.; Misra, S. K. Magn Reson Chem 1991, 29, 749; (b) Hughes, D. W.; Nalliah, B. C.; Holland, H. L.; Maclean, D. B. Can J Chem 1977, 55, 3304.

[31] Singh, S. P.; Sehgal, S.; Tarar, L. S. Indian J Chem B 1989, 28, 27.

[32] (a) Thakar, A. S.; Singh, K. K.; Joshi, K. T.; Pancholi, A. M.; Pandya, K. S. E-J Chem 2010, 7, 1396; (b) Sonnenschein, R. N.; Johnson, T. A.; Tenney, K.; Valeriote, F. A.; Crews, P. J Nat Prod 2006, 69, 145.

[33] Pandey, K. S.; Khan, N. Arch Pharm Chem Life Sci 2008, 341, 418.

[34] (a) Rahman, M. M.; Mosaddik, A.; Wahed, M. I. I.; Haque, M. E. Fitoterapia 2000, 71, 704; (b) Mosaddik, M. A.; Haque, M. E. Phytother Res 2003, 17, 1155.

[35] (a) Denisova, A. B.; Glukhareva, T. V.; Andronnikova, G. P.; Mokrushin, V. S.; Dehaen, W.; Luyten, I.; Sosnovskikh, V. Y.; Meervelt, V.; Bakulev, V. A. J Chem Res 2001, S, 12; (b) Denisova, A. B.; Glukhareva, T. V.; Andronnikova, G. P.; Mokrushin, V. S.; Dehaen, W.; Luyten, I.; Sosnovskikh, V. Y.; Meervelt, V.; Bakulev, V. A. J Chem Res 2001, M, 0133.